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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,814	MARCHE ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,12 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 June 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/05/2006;02/26/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-18, in the reply filed on 05/06/2009 is acknowledged. The traversal is on the ground(s) that the prior art references cited by the examiner to demonstrate lack of unity were "directed to separate subject matter" and therefore there was "no reason to combine the cited references". This is not found persuasive because the only apparent difference between the subject matter of the two references is the species on which the methods were performed: Morley amplified a human TCR gene whereas Pasqual amplified a mouse TCR gene. This is not "separate" subject matter, and what is taught in one reference was clearly applicable to the other.

Applicant's election with traverse of species A1, claim 8, and B3, claim 13, in the reply filed on 05/06/2009 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant is correct in the understanding that the examiner will begin with a search of the elected species. If the elected species is free of the art, the examiner will search the non-elected species. Moreover, if a generic claim is free of the art, the non-elected species will be rejoined. The examiner has, however, rejoined claims 10 and 11, since the primary reference Pasqual taught Southern blot, and claims 10 and 11 are obvious in view of the cited art.

The requirement, to the extent it has been maintained, is still deemed proper and is therefore made FINAL.

Claims 9, 12 and 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/06/2009.

Information Disclosure Statement

One reference (FR 2 671 356 A) on the information disclosure statement filed 06/05/2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because no English translation has been provided. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Drawings

The drawings are objected to because figures 4 and 5 contain shading which obscures text, making the text unreadable. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must

be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Sequence Compliance

Figure 5 displays nucleic acid sequences falling within the definitions set forth in 37 CFR 1.821 through 1.825. As noted in MPEP 2422.01, any unbranched nucleic acid sequence having 10 nucleotides or more, and specifying at least 4 nucleotides (i.e. nucleotides other than "n"), fall within these definitions. In addition, MPEP 2422.02 states: "...when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings."

37 CFR 1.821(c) requires:

"Patent applications which contain disclosures of nucleotide and /or amino acid sequences must contain, as a separate part of the disclosure, a paper copy disclosing the nucleotide and /or amino acid sequences and associated information using the

symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper copy is hereinafter referred to as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing." Each sequence set forth in the "Sequence Listing" shall be assigned a separate sequence identifier. The sequence identifiers shall begin with 1 and increase sequentially by integers."

37 CFR 1.821(d) requires:

"Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Accordingly, any sequence having more than 10 nucleotides, at least 4 of which are specified (i.e. not being "n"), should appear in the Sequence Listing and should also be presented with the corresponding SEQ ID NO. This would apply to sequences found in figure 5 (specifically, those sequences in the column labeled "Spacer"; the sequences in the columns labeled "Heptamer" and "Nonamer" are less than 10 nucleotides and thus exempt from the requirement).

Please consult MPEP 2426 for information regarding amendments to/replacements of the Sequence Listing and computer readable copy thereof.

Finally, as set forth in MPEP 2421.03:

"Upon detection of damage or a deficiency, a notice will be sent to the applicant detailing the damage or deficiency and setting at least a 30-day period for reply. The

period for reply will usually be 2 months when sent during the preexamination processing of an application. However, if the notice is sent out with an Office communication having a longer period for reply, the period for reply may be longer than 2 months, e.g., where the notice is sent with an Office action on the merits setting a 3-month period for reply. Extensions of time in which to reply will be available pursuant to 37 CFR 1.136."

Accordingly, the period for reply for compliance with the Sequence Rules will run concurrently with the period for reply to this Office action on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 11 and 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 recite "between a few hundred base pairs and several tens of kb in size". The metes and bounds of the claims are unclear, since this phrase does not clearly demarcate the scope of the claim. Reasonable people could disagree whether, for example, 200, 250 or 320 base pairs, or 80, 95, 150 or 500 kb falls within the range of "between a few hundred base pairs and several tens of kb in size". As all claims under examination depend ultimately from claim 1, they are rejected for the same reasons.

Also, the language of claims 1 and 2 that the primers are "selected so as to correspond to the following characteristics" is vague and indefinite. While it can be understood what is meant by "selected so as to *have* the following characteristics", it is unclear what is meant by "*correspond to* the following characteristics".

In addition, the language of claims 1 and 2 that the polymerase or mixture of polymerases has a correction activity "that makes it possible to substantially improve elongation" is vague and indefinite, as it is unclear what in particular is required by this language. Would *any* amount of correction activity "substantially improve" elongation? And just how much of an improvement (and relative to what) would be considered "substantially improved"? Simply leaving it at "having a correction activity" would be more favorably considered.

Also, with regard claim 2, the last step (d) is vague and indefinite. Based on paragraph [0008] of the published application (US 2008/0166704), it appears that not all recombined VJ segments have a D segment: "This functional gene consists of the C region and of a combination of a V and of a J (and optionally D), which constitutes the molecular identity mark of the lymphocyte and the molecular basis of the specificity of the antigen receptor." Therefore, it is not clear whether claim 2 is limited to detection of recombined VDJ segments only, or whether the claim is intended to encompass detection of recombined VJ and/or VDJ segments. Appropriate clarification is required.

Also with regard to claim 2, the language "corresponding to a V segment of the variable domain of the α chain of a T-cell receptor" and "corresponding to a J segment of the α chain of a T-cell receptor" is vague and indefinite. The V_x and J_y genes either

are, or are not, V and J segments, respectively, of the α chain of a T-cell receptor. Applicant is advised to replace "corresponding to" with "said V_x gene being" and "said J_y gene being".

Claims 3 and 8 are rejected under this section on additional grounds:

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "systematic analysis of the entire locus concerned", and the claim also recites "in particular of the human TCRAD locus" which is the narrower statement of the limitation. Similarly, claim 3 recites "elimination of the primers forming autodimers or stable hairpins" and the claim also recites "in particular by analysis with a suitable software". Likewise, claim 8 recites the limitation "by electrophoretic migration on a

gel", and the claim also recites "preferably pulsed-field migration", which is the narrower statement of the limitation.

Claims 5, 13 and 14 are rejected under this section on additional grounds. The claims recite limitations following the term "advantageously". It is unclear whether the claims require what follows the term "advantageously". A limitation in a claim is either required, or it is not. Applicant is advised to strike the "advantageously" language and simply and clearly state what the claim requires. With regard to the term "optionally" used in claim 5, the limitation following that term is construed simply as an optional limitation (i.e. not required by the claim). The examiner has no objection to the presence of the term "optionally", however, the limitation following this term confers no patentable weight. Applicant's attention is drawn to the fact that, should claims 10-12 ultimately be rejoined, they will be subject to the same rejection based on the "advantageously" language. Therefore, Applicant may wish to consider addressing the limitation in these claims as well.

Claim 6 is rejected under this section on additional grounds. Claim 6 recites "the multiplex long PCR (LPCR)". Claim 6 depends from claim 1, which does not recite a "long multiplex PCR" but rather "multiplex PCR" (step b). Claim 2, however, recites "long multiplex PCR" at step b. Applicant is advised to recite "multiplex long PCR" in claim 1, step b, to provide proper antecedent basis for this limitation in claim 6.

Claims 15 and 16 are rejected under this section on additional grounds. It is unclear what would constitute a "standard immune repertoire".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 8, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007). Note that as the GenBank reference is so large, only selected pages have been provided with this Office action.

With regard to claims 1 and 2, Pasqual taught a method for the quantitative evaluation of the immune repertoire of an individual by genetic rearrangement (specifically, TCRAD diversity). The method comprised extraction of genomic DNA from a biological sample (paragraph spanning pages 1164-5). The method comprised amplification of a segment of said genomic DNA between a few hundred base pairs and several tens of kb in size by multiplex long PCR (paragraph spanning pages 1164-5: maximum amplicon size was ~5 kb; see also figure 1). The primers used in Pasqual's method comprised "V" primers and "J" primers (paragraph spanning pages 1164-5). Since the V gene RSS flanks the 3' end (i.e. lies downstream) of the V gene and the J gene RSS flanks the 5' end (i.e. lies upstream) of the J gene (see figure 4, Krangel, Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007), Pasqual's V primer inherently hybridized upstream of the RSS of the V gene, while the J primer inherently hybridized downstream of the RSS sequence of the J gene.

Pasqual's method used the Expand High Fidelity PCR system (paragraph spanning pages 1164-5). As evidenced by the Biochemica article, the Expand High Fidelity PCR system is a blend of Taq and Pwo polymerases, the latter having proofreading (i.e. correction) activity, the blend substantially improving elongation. Therefore, Pasqual's method inherently met this limitation.

Pasqual's amplification comprised an initial denaturing step (paragraph spanning pages 1164-5: 5 min at 94°C) and cycles of denaturation, hybridization and elongation (at 72°C, for six minutes; paragraph spanning pages 1164-5).

Pasqual's method comprised separation of amplified fragments (page 1165, first full paragraph: separation by agarose gel electrophoresis).

Pasqual's method also comprised detection of the recombined VJ segments (page 1165, first full paragraph: Southern blot of the gel followed by hybridization with probes).

With regard to claim 3, Pasqual taught using primers "specific" for given V_x and J_y genes (paragraph spanning pages 1164-5). This implicitly teaches selection of primers whose 3'OH ends are complementary only to the regions of interest.

With regard to claim 6, Pasqual performed PCR on purified (i.e. extracted) genomic DNA (paragraph spanning pages 1164-5).

With regard to claim 8, Pasqual's method comprised electrophoretic separation of amplified fragments on a gel (page 1165, first full paragraph).

With regard to claims 17 and 18, Pasqual taught T lymphocytes (T cells) from thymus (i.e. thymocytes).

With regard to claims 1 and 2, Pasqual did not perform the method on human genomic DNA (but rather, mouse genomic DNA). Pasqual did not perform the elongation steps of the PCR for 10 minutes. Pasqual performed only the final elongation step for 10 minutes (the claims require "steps", plural). Pasqual performed the other elongation steps for 6 minutes (paragraph spanning pages 1164-5).

With regard to claim 3, Pasqual did not teach "systematic analysis of the entire locus concerned, and in particular of the human TCRAD locus, using suitable software".

Nor did Pasqual teach elimination of primers forming autodimers or stable hairpins or primers that form hybrids with one another.

With regard to claim 4, Pasqual did not teach primers selected from SEQ ID NOs: 1-21.

GenBank GI:21363121 disclosed the sequence of the human T cell receptor alpha/delta locus on chromosome 14. At least SEQ ID NOs: 1 and 11 (and presumably all the other SEQ ID NOs from 1-21) are found within the sequence disclosed by GenBank GI:21363121:

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GenBank          128261  GGTCGTTTTTCTTCATTCCTTAGTCG  128286
                         |||||||||||||||||||||||||
SEQ ID NO:1      1       GGTCGTTTTTCTTCATTCCTTAGTCG  26


GenBank          989703  GTAAGTTTGAAGGGAGTGGGGGAAG  989727
                         |||||||||||||||||||||||||
SEQ ID NO:11     25      GTAAGTTTGAAGGGAGTGGGGGAAG  1
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Wu taught selection of specific primer pairs and probes for analyzing specific analytes (see title). Wu taught (beginning at column 18, line 50: "PRIMER OPTIMIZATION"):

"An analysis and modification of the original primers was undertaken with the objectives of improving the amplification efficiency of each primer and decreasing the possibility of cross-reactivity among the primer pairs. Several parameters were manipulated in order to minimize physical property differences among the primers. Each primer was modified to approximately the same length, i.e., 19-24 bp. Primer oligonucleotides of this length result in greater specificity in the amplification reaction while shorter primers may result in the amplification of non-specific products. Because the efficiency of the primer pairs is also effected by the presence of hairpin loops and dimers, OLIGO 5.0 software (NBI, Plymouth, Minn., USA) was used to analyze potential primers. If hairpin loops or dimers were found, the primer sequence was modified to remove them or to, at least, diminish the effect."

Arstila taught amplification of human complementary DNA (cDNA, i.e. not genomic DNA) for analysis of T cell receptor αβ diversity (see entire article, e.g. page 958, 2nd column, last paragraph; page 959, paragraph spanning columns 2-3).

It would have been *prima facie* obvious to one or ordinary skill in the art at the time the invention was made to apply the method taught by Pasqual for analyzing T cell receptor diversity to humans. One would have been motivated to do this because it was clearly of interest to those skilled in the art to assess human T cell receptor diversity, as shown by the disclosure of Arstila. Pasqual stated (abstract): "Knowledge of the complete nucleotide sequence of the mouse TCRAD locus allows an accurate determination V-J rearrangement status." Likewise, one of ordinary skill would have reasoned that knowledge of the complete sequence of the human TCRAD locus (as disclosed by GenBank GI:21363121) would allow similar analysis of human T cell receptor V-J rearrangements. Hence one would have been motivated to use the known human sequence to select appropriate primers for the various V and J segments, just as Pasqual did for the mouse. Using primer design software, and choosing primers that were specific, free of secondary structure, and that were unlikely to form dimers (either autodimers or heterodimers with other primers being used) were well-known principles in the art of designing primers, as shown by the disclosure of Wu. Pasqual's method offered an advantage over the earlier method of Arstila, in that the latter artisan's method was based on amplification of cDNA (i.e. analysis at the transcriptional level) and for only specific V and J genes. Pasqual addressed these shortcomings (page 1164, column 2, 1st and 2nd paragraphs): "Finally to date, available informations

encompass essentially either analysis at the transcriptional level or gene analysis for only a few V families, thus precluding a general synthetic overview of gene rearrangements. In this report, to eliminate the biases due to transcriptional regulation…we have used a sensitive multiplex PCR assay at the genomic DNA level." Hence one would have been motivated to supplant the approach used by Arstila with the technique of Pasqual to study human TCR diversity, to avoid bias caused by transcriptional regulation and provide a general synthetic overview of gene rearrangements. The only remaining difference between the combined teachings of the references and the claimed methods is using a 10 minute extension step rather than a 6 minute extension step. One of skill in the art would have understood that longer extension steps allowed for amplification of longer fragments, so it would have been reasonable to use 10 minutes (or longer) for the extension steps (as opposed to just the last extension step, which Pasqual did).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of

GenBank GI:21536269 [online] June 21, 2002 [retrieved on October 27, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21536269:OLD03:2443019. As the GenBank references are so large, only selected pages have been provided with this Office action.

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed.

With regard to claim 5, while Pasqual did not analyze V, D or J segments of the TCR β chains, Arstila did analyze TCR β chain gene rearrangement by PCR with primers to specific V_β and J_β segments (e.g. page 958, 2nd column, last paragraph).

GenBank GI: 21536269 disclosed the complete sequence of the human TCR β locus.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Pasqual for analyzing T cell receptor diversity to human TCR β chain gene rearrangements. Those of skill in the art were interested in such analyses as shown by the disclosure of Arstila. Pasqual stated (abstract): "Knowledge of the complete nucleotide sequence of the mouse TCRAD locus allows an accurate determination V-J rearrangement status." Likewise, one of ordinary skill would have reasoned that knowledge of the complete sequence of the human TCR β locus (as disclosed by GenBank GI:21536269) would allow similar analysis of human T cell receptor β chain V(D)J rearrangements.

Pasqual's method offered an advantage over the earlier method of Arstila, in that the latter artisan's method was based on amplification of cDNA (i.e. analysis at the transcriptional level) and for only specific V and J genes. Pasqual addressed these

shortcomings (page 1164, column 2, 1st and 2nd paragraphs): "Finally to date, available informations encompass essentially either analysis at the transcriptional level or gene analysis for only a few V families, thus precluding a general synthetic overview of gene rearrangements. In this report, to eliminate the biases due to transcriptional regulation…we have used a sensitive multiplex PCR assay at the genomic DNA level." Hence one would have been motivated to supplant the approach used by Arstila with the technique of Pasqual to study human TCR diversity, to avoid bias caused by transcriptional regulation and provide a general synthetic overview of gene rearrangements.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of Liljedahl et al (US 2003/0153044) and Perron et al (US 2003/0198647).

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed. These references did not teach or suggest incrementing the elongation steps by 15-20 seconds per cycle.

Liljedahl taught PCR using the Expand system and stated (paragraph [0151]): "Progressively longer elongation steps are used to increase the chances of amplifying longer DNA inserts."

Perron taught PCR using the Expand system, and incremented each elongation step by 20 seconds (paragraph [0374]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to increment the elongation steps by 15-20 seconds each cycle when practicing the method suggested by the combined teachings of Pasqual, GenBank GI:21363121, Wu and Arstila, since this procedure was known and used in the art when amplifying long templates.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of Shah et al (US 5,519,127).

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed. Pasqual taught Southern blotting and hybridization with radioactively

labeled oligonucleotide probes (page 1165, second paragraph; see also figure 1). Pasqual did not specifically teach that a nylon membrane was employed (as recited in claim 10) or a probe selected from SEQ ID NOs:23-37 (as recited in claim 11).

GenBank GI:21363121 disclosed the sequence of the human T cell receptor alpha/delta locus on chromosome 14. At least SEQ ID NO: 22 (and presumably all the other SEQ ID NOs from 22-37) are found within the sequence disclosed by GenBank GI:21363121:

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GenBank          128263  TCGTTTTTCTTCATTCCTTAGTCG  128286
                         ||||||||||||||||||||||||
SEQ ID NO:22     1       TCGTTTTTCTTCATTCCTTAGTCG  24
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Shah taught (column 8, lines 33-40): "Southern blot analysis, in accordance with well known procedures, involves size fractionating DNA on acrylamide or agarose gels, denaturing the DNA in the gels and then transferring and immobilizing the DNA from the gel onto a filter such as nitrocellulose, nylon, or other derivatized membranes (which readily can be obtained commercially, specifically for this purpose) either by electrophoresis or capillary action (i.e " blotting")."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a nylon membrane when practicing the method suggested by the combined teachings of Pasqual, GenBank GI:21363121, Wu and Arstila, as this would have represented nothing more than selecting a known material for its art-recognized purpose (MPEP 2144.07). The rationale to apply the method of Pasqual to human T cell receptor gene rearrangements has been discussed (see rejection of claims 1-4, 6, 8, 17 and 18 above). Therefore, it would also have been

obvious to select probes for the Southern blotting from the known sequence of the human TCRAD locus disclosed in GenBank GI:21363121.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of Barber (US 2002/0099015).

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed. Pasqual taught Southern blotting and hybridization with radioactively labeled oligonucleotide probes (page 1165, second paragraph; see also figure 1). Pasqual did not teach detection with a DNA labeling agent during the migration, and detecting after UV excitation.

Barber taught (paragraph [0247]): "Following PCR, 10 µl of each sample was analyzed on a 1% ethidium bromide agarose gel and the products visualized by ultraviolet light. If products were visible, the gel was usually subjected to southern blotting with end-labelled oligonucleotides and the products visualized by autoradiography."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include ethidium bromide in the agarose gels used to separate the PCR products when practicing the method suggested by the combined teachings of Pasqual, GenBank GI:21363121, Wu and Arstila. One would have been motivated to do this in order to visualize the PCR products on the gel to ensure the PCR had been successful, prior to investing more time and effort in carrying out the blotting and hybridization procedure.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of 02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of Stahl (US 2003/0003459).

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed. Pasqual taught Southern blotting and hybridization with radioactively labeled oligonucleotide probes (page 1165, second paragraph; see also figure 1). Pasqual did not teach detection by labeling the primers with flourochromes during the amplification.

Stahl taught (paragraph [0010]): "Multiplexing often generates PCR products that overlap in size, making them difficult to separate. However, multiplexed PCR is greatly enhanced by the use of fluorescent labeling technology. By attaching different fluorescent labels to PCR primers, a scanning laser can be used to distinguish the different alleles by different wavelengths, even when their sizes overlap."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method suggested by the combined teachings of Pasqual, GenBank GI:21363121, Wu and Arstila by labeling the different primers used in the multiplex PCR with different fluorescent labels as suggested by Stahl to allow the products of the different primers to be distinguished based on the unique labels, so as to distinguish among amplified fragments that were similar in size. In addition, the use of fluorescent labels rather than the radioactive detection used by Pasqual would have avoided the safety and disposal issues associated with radioactive materials.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pasqual et al (J Exp Med 196(9):1163-73, Nov 2002, cited on the IDS of 06/05/2006) [as evidenced by Biochemica (No. 3, pp. 4-5, 1995) and Krangel (Nature Immunology 4(7):624-630, July 2003, cited on the IDS of 02/26/2007)] in view of GenBank GI:21363121 [online] June 10, 2002 [retrieved on October 26, 2009] retrieved from http://www.ncbi.nlm.nih.gov/sviewer/viewer.fcgi?21363121:OLD03:2443007, Wu et al (US 5,756,701) and Arstila et al (Science 286:958-61, October 1999, cited on the IDS of

02/26/2007) as applied to claims 1-4, 6, 8, 17 and 18 above, and further in view of Dau et al (US 6,087,096).

The teachings of Pasqual, GenBank GI:21363121, Wu and Arstila have been discussed. These references did not teach analyzing T-cell receptor profiles (repertoire) for the purpose of monitoring a pathology or a response to treatment in a subject, or comparing the profile of a subject to a "standard immune repertoire".

Dau taught (paragraph spanning pages 13-14):

"The ability to characterize an individual's T cell repertoire has practical applications for monitoring treatments for innumerable disorders, because the efficacy of many treatments lies in their ability to modulate (to potentiate or to suppress) an immune response. For example, when an individual is afflicted with many disorders (e.g., neoplastic disorders, chronic infection), it is desirable to provide a treatment designed to potentiate the individual's own immune response to the disorder, to suppress or overcome the disorder (i.e., it is desirable to provide an immunoproliferative treatment). A method for characterizing an individual's T cell repertoire which detects a T cell immunoproliferative response to a treatment is useful for monitoring the efficacy of such a treatment. A first characterization of the T cell repertoire as it exists prior to the treatment is compared to a second characterization of the T cell repertoire during or after the treatment to detect the presence or absence of a T cell immunoproliferative response to the treatment. Characterizations may be repeated to continue to monitor the treatment and/or to monitor for a relapse of the disorder between treatments."

Dau also taught comparing the T cell repertoire in a subject to that of a healthy human subject (paragraph spanning columns 3-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the method for analyzing human TCR profiles suggested by the combined teachings of Pasqual, GenBank GI:21363121, Wu and Arstila for the purpose of monitoring response to treatment (which also represents "phases of pathology") in an individual, since it was known in the prior art as taught by

Dau to use TCR profiles as an indication of response to treatment by comparing pre- and post-treatment TCR profiles, as well as to use TCR profiles as an indication of the presence of disease by comparing an individual's TCR profile to that of a healthy individual (i.e. standard immune repertoire).

Conclusion

In conclusion, Pasqual taught a general method employing multiplex PCR of genomic DNA, using specific primers directed to V and J gene segments of the mouse TCRAD locus to analyze gene rearrangements responsible for the generation of TCR (T cell receptor) diversity. It would have been obvious to those of skill in the art to employ this strategy to analyze T cell receptor gene rearrangements in other species, including humans, where the sequences of the relevant loci were known, thus allowing the selection of appropriate primers and probes for carrying out the method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637